REMARKS/ARGUMENTS

With this request for reconsideration, claims 15-17 and 20-21 are pending. For convenience, the Examiner's rejections are addressed in the order presented in the July 28, 2004 Office Action. Applicants thank Examiner Flood for her time in conducting an interview with Applicants' representative, Beth Kelly, on January 14, 2005. Rejections for alleged lack of utility, enablement and written description were discussed, but no agreement was reached.

I. Rejections under 35 U.S.C. §101

Claims 15-17, 20, and 21 are rejected under 35 U.S.C. §101 for allegedly lacking an apparent or disclosed specific and substantial credible utility. The Office Action states that the application provides a description of an R0101 protein and an isolated DNA encoding such protein, but alleges that the specification does not provide the biological role or significance of the protein. Applicants respectfully traverse the rejection. The claims are directed to methods of screening for a bioactive agent that binds a cell cycle protein. The application as written provides both a disclosed specific and substantial credible utility and a well established utility for the claimed invention.

A. The application provides a specific and substantial utility for the claimed invention.

The application as filed provides a specific utility for the claimed invention. The specification asserts that changes in expression levels of R0101 proteins and encoding nucleic acids can be used to diagnose cell cycle associated disorders (which specifically include cancer) or to determine prognosis of such disorders. (Specification at page 41, lines 21-23; and at page 40, lines 23-24.) Moreover the specification provides evidence that R0101 is overexpressed in certain cancers, including, *e.g.*, breast, uterine, cervical, brain, kidney, lung, and esophageal. See, *e.g.*, Figure 5 and legend.

According to the MPEP, "[a] specific utility is 'specific' to the subject matter claimed." MPEP 2107.01. Here, the specific asserted utility is diagnosis or determination of

prognosis of the specific disease cancer. Additional disclosure in the specification, discloses data sufficient to support diagnosis or determination of prognosis of cancer in specific organ systems, *e.g.*, breast, uterus, cervix, brain, kidney, lung, and esophagus. Thus, the application provides a specific utility for the claimed invention.

The application as filed also provides a substantial utility for the claimed invention. According to the MPEP, "[a] 'substantial utility' defines a 'real world' use." MPEP 2107.01. One example of a real world use is the following: "An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use in identifying potential candidates for preventive measures or further monitoring." *Id.* Here, the inventors have provided the first evidence that R0101 is overexpressed in some tumors, when compared to normal tissues. *See, e.g.*, Specification at Figure 5 and legend. Thus, the identification of bioactive agents that bind to R0101 protein and that can be used for diagnosis or determination of prognosis of cancer is a substantial utility.

B. The asserted utility is a credible utility.

The utility asserted in the application is a credible utility and is supported by experimental evidence in the application at Figure 5. An assertion of utility in an application must be presumed to be true by the patent office. MPEP 2107.02; *citing In re Langer,* 183 USPQ 288 (CCPA 1974) and *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). "[T]o overcome the presumption of truth that an assertion of utility by the applicant enjoys, Office personnel must establish that it is more likely than not that one of ordinary skill in the art would doubt (*i.e.*, 'question') the truth of the statement of utility." MPEP 2107.02; *citing In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The Examiner has not done so.

First, the application as filed provides evidence of the asserted utility at Figure 5 and its legend, which demonstrate that R0101 is overexpressed in certain cancers. Applicants have provided declaratory evidence, with this response and a previous response, that those of skill would find the asserted utility to more likely than not be true. Applicants have also provided a reference, Yu *et al.*, *Oncogene* 20:484-489 (2001), which supports the asserted utility.

The Examiner has not provided any convincing reasoning or evidence to refute the evidence of utility found in the specification, in Yu *et al.*, or in the declarations filed with this or previous responses.

Applicants provided with this response a declaration from Dr. Yasumichi Hitoshi, marked as Exhibit A, stating again for the record, that based on the evidence provided in the specification at Figure 5, those of skill would believe the asserted utility to be true. Dr. Hitoshi states that, based on Figure 5 and its legend, those of skill would understand that R0101 is overexpressed in certain cancer cells relative to untransformed cells from the same tissue. In addition, Dr. Hitoshi asserts that based on the overexpression data, those of skill would recognize that measurement of R0101 levels would be useful as a diagnostic or prognostic indicator of those cancers. Dr. Hitoshi also addresses objections to the Yu *et al.* reference raised in the Office Action. The Office Action characterizes Yu *et al.* as a post-filing reference and asserts that it cannot be used to support the asserted utility. Dr. Hitoshi states that the authors of Yu *et al.* include the inventors of the claimed invention and that data on overexpression of R0101 disclosed in Yu *et al.* is the same data found in some of the figures filed with the invention, *e.g.*, Figure 5. Thus, the Examiner has improperly characterized Yu *et al.* as a post-filing reference, because data included in the application is also included in Yu *et al.* Yu *et al.* is provided to demonstrate that a peer reviewed journal also found the data from the application relevant and its interpretation believable. Thus, applicants have provided evidence from Dr. Hitoshi and from a peer-reviewed journal that the asserted utility would more likely than not be believed to be true by those of skill.

The Office Action at page 7 asserts that overexpression of R0101 could merely be "a result of an increase in metabolic protein activity." First, the Office Action provides no explanation or reference to indicate exactly what is meant by "metabolic protein activity", or how it relates to cancer diagnosis and prognosis. Moreover, Dr. Hitoshi asserts in his declaration that because the inventors compared R0101 expression to that of a control protein and that based on the comparison of R0101 levels to those of the control protein, the R0101 overexpression data is specific for certain cancers, *e.g.*, those with demonstrated overexpression in Figure 5.

The Office Action also asserts that, because Yu *et al.* disclose that R0101 "may" have prognostic significance, the reference does not support the asserted utility. As set forth the holdings of the Federal Circuit Court of Appeals and summarized by MPEP, this assertion improperly evaluates the evidence submitted by the Applicants in support of utility. Use of the word "may" is proper and provides sufficient evidence of the truth of the assertion of utility in the eyes of those of skill. The proper standard for evaluation of evidence of utility follows.

> There is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed . . ., and whether the asserted utility appears to contravene established scientific principles and beliefs. . . Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." . . . Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. . . Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.
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> MPEP 2107.02.VII, *citations omitted.*

Nothing in Yu *et al.* or in the reasoning presented in the Office Actions has demonstrated that those of skill would not believe the asserted utility to be true based on the information in the specification or the evidence provided to support it during prosecution. Therefore, the utility asserted in the application must be presumed to be credible by USPTO personnel.

C. The asserted utility is a well established utility.

Applicants also assert that use of agents that bind to the R0101 protein to diagnose or provide prognostic information on cancer is a well established utility. The Office Action continues to allege that no function for R0101 has been provided. Applicants continue to assert that a function for R0101 is provided by its ability to bind to the PCNA protein and

information on the PCNA protein known in the art, and by a model of R0101 found in Figure 9. However, even if no specific biological function for R0101 is provided, based on the demonstration that R0101 is overexpressed in certain cancers and according to the Revised Interim Utility Guidelines Training Materials, a well established utility for the claimed invention has been asserted.

Applicants also draw the Examiner's attention to the Revised Interim Utility Guidelines Training Materials (1999) (available at http://www.uspto.gov/web/menu/utility.pdf), Example 12, pages 69-70. This example is analogous to claimed invention. Example 12 discloses a protein X, isolated from a cell, that binds to receptor A. No functions are provided for protein X or receptor A. However, the specification demonstrates that receptor A is overexpressed in a particular cancer, *i.e.*, in melanoma cells. As analyzed by the Utility Guidelines, a well established utility is provided for claims directed to Receptor A, methods to identify agents that bind to Receptor A complexed to protein X, and a monoclonal antibody that binds to Receptor A, because of the demonstration of overexpression receptor A in certain cancer cells. The Guidelines go on to state that the overexpression data provides a correlation between the claimed method and diagnosis of melanoma, *i.e.*, cancer.

Similar analysis can be applied to the present claims. The specification provides evidence that, like Receptor A, R0101 is overexpressed in certain cancer cells. The claims are directed to methods of identifying agents that bind to R0101, wherein R0101 binds to PCNA. Unlike protein X, PCNA has a well known role in DNA replication and in carcinogenesis. The Utility Guidelines insist that evidence of overexpression of a protein in cancer cells, but not normal cells provides a well established utility. The Office is required to abide by published policy. *Morton v. Ruiz*, 415 U.S. 199, 235 (1974) ("it is incumbent upon agencies to follow their own procedures"). Thus, the claimed invention has a well established utility.

Applicants have provided evidence and arguments that the claimed invention has specific and substantial credible utility and a well established utility. Based on the above arguments and evidence, withdrawal of the rejection for alleged lack of utility is respectfully requested.

II. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 15-17 and 20-21 are rejected under 35 U.S.C. §112, first paragraph, for allegedly failing to teach how to use the invention using the reasoning given in the enablement rejection. Applicants respectfully assert that the arguments against the utility rejection in part I of this response, can be used to overcome this rejection under 35 U.S.C. §112, first paragraph.

Claims 15-17 and 20-21 are also rejected under 35 U.S.C. §112, first paragraph, because allegedly experimentation without reasonable expectation of success and an enormous burden are required of those of skill to practice the invention. The Office Action also asserts that practice of the claimed methods is beyond those of skill because, allegedly, "there is no way of determining whether the protein corresponding to SEQ ID NO:2 corresponds to any known protein with known activity, but for which the sequence is unknown." Office Action at page 9. Applicants traverse the rejection.

As set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether... it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

Assays to determine binding are well described in the specification. For example, the specification at page 27, line 32 through page 30, line 32, discloses binding assays where, *e.g.*, R0101 protein is bound to a solid support and a candidate bioactive agent is added, preferably including a detectable label. Excess agent is washed from the R0101 protein and the amount of label is assayed in order to determine whether binding has occurred. Variations of the assays are described, including competitive assays.

At Figure 2, Applicants also identify the sequence of a PCNA binding site in the R0101 protein and alignments of that biding site with PCNA binding sites from other known PCNA binding proteins. At Figures 8 and 9, Applicants disclose that, like other PCNA binding

proteins, R0101 binds to cyclin dependent kinases. Also at Figure 8, Applicants provide data on which portion of the R0101 protein are necessary for binding to PCNA. Thus, Applicants disclose both structural and functional information on the R0101 protein in the specification.

The Office Action alleges that no "substantial and credible" nexus has been established between overexpression of R0101 and cancer. This is incorrect. As indicated by Dr. Hitoshi, on viewing Figure 5 of the specification, those of skill would understand that determination of the level of R0101 could be used to provide diagnostic or prognostic information on certain cancers. The Office Action also asserts that R0101 could be a "metabolically active protein." As argued in Section I of this response, the Office Action provides no explanation or reference to indicate exactly what is meant by "metabolic protein activity", or how it relates to cancer diagnosis and prognosis. Moreover, Dr. Hitoshi asserts in his declaration that the R0101 overexpression data is specific for certain cancers, *e.g.*, those with demonstrated overexpression in Figure 5. Thus, the information in the specification is sufficient to provide the "substantial and credible" nexus between overexpression of R0101 and cancer. Based on the information in the specification, those of skill would understand how to identify and use agents that bind to the R0101 protein for diagnosis or determination of prognosis of certain cancers.

Applicants respectfully bring to the Examiner's attention two recent decisions by the Board of Patent Appeals and Interferences: *Ex parte Sun,* Appeal No. 2003-1993 and *Ex parte Bandman*, Appeal No. 2004-2319. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were enabled because the supporting specifications provided a single reference sequence and an assay for activity of the encoded protein.

In view of the above amendments and remarks, Applicants respectfully request withdrawal of claim rejections for alleged lack of enablement.

III. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 15-17, and 20-21 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification as filed.

According to the Office Action, the description is not adequate because allegedly 1) no description is given of experimentation of combining the R0101 protein with a candidate bioactive agent and 2) the generic claim lacks a representative number of species for support. Applicants respectfully traverse the rejection.

With respect to the alleged lack of description of the binding assays, Applicants provide a declaration from Dr. Yasumichi Hitoshi, stating that the specification as written is sufficient for those of skill to practice the claimed invention. The specification provides description of binding assays in vitro, *e.g.*, at page 27, line 32 through page 30, line 32, and description of two hybrid assays, *e.g.*, at page39, line3 through page 40, line 3. Thus, the specification defines a binding event. The Office Action appears to allege that an example of a binding event is required and that a biological function must be assigned to the R0101 protein. First, this is not the applicable standard for written description. In addition, the specification demonstrates that the R0101 protein is overexpressed in certain cancers and that the R0101 protein binds to the PCNA protein. This is sufficient to provide a function and a utility for the R0101 protein. Therefore, the specification does provide the required description of the claimed assays for screening for a bioactive agent that binds to R0101.

The Office Action also asserts that claim 15, reciting proteins with 95% identity to SEQ ID NO:2, lacks description because allegedly a sufficient number of species is not found in the specification to support the generic claim. Applicant traverse this rejection. In addition, in an interview on January 14, 2005 with Applicants' representative Beth Kelly, Examiner Flood expressed the opinion that an example of a protein with 95% identity to the reference sequence is required to fulfill the written description requirement. This is simply not the standard for written description under US patent law.

As currently applied, the specification does comply with US patent law for description of a nucleic acid or amino acid sequence. The Federal Circuit court of Appeals addressed the description adequate to show one of skill that the inventors were in possession of a claimed genus at the time of filing. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). An applicant may also show that an invention is complete by

> . . . disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Id.* at 1613.

Furthermore, "description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *See, e.g.*, 66 Fed. Reg. 1099, 1106 (2001).

As indicated above, the specification provides a very detailed description of the amino acid sequence of the R0101 protein, *e.g.*, SEQ ID NO:2. Assays to identify functional R0101 proteins that bind to proteins such as PCNA or CDK proteins are disclosed. S*ee, e.g.*, Figure 8. The specification also provides alignments of the PCNA binding domain of R0101 with PCNA binding domains from known PCNA proteins at Figure 2B.

The Examiner has failed to provide any reason why a skilled person, who is aware of the disclosed specific amino acid sequence of R0101 and the disclosed assays of R0101 function, would be unable to recognize that the Applicants invented the claimed invention, including use of proteins with at least 95% identity to SEQ ID NO:2.

Applicants again bring to the Examiner's attention the *Sun* and *Bandman* decisions by the Board of Patent Appeals and Interferences. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were described because the supporting specifications provided a single reference sequence, teachings of areas of the claimed sequences that could be modified, and a functional assay for activity of the encoded proteins. Such teachings are included in the present application, as indicated above.

Applicants also direct the Examiner's attention to Example 14 of the Synopsis of Application of Written Description Guidelines which analyzes a claim directed to a protein having an amino acid sequence at least 95% identical to SEQ ID NO:3 and that has a specific activity. In these Guidelines, the Patent Office concluded that the claim was adequately described within the meaning of 35 U.S.C. §112, first paragraph. The R0101 protein does have PCNA binding activity as demonstrated in Figure 8. Therefore, on the basis of Written

Description Guidelines issued by the USPTO, the present claims directed to sequences that are 95% identical to SEQ ID NO:2, meet the written description requirement.

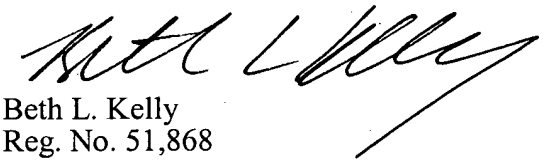
In view of the above amendments and arguments, Applicants, respectfully request withdrawal of the rejection for alleged lack of written description.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments
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